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[IT/US]; 52 Pepperbush Lane, Guilford, CT 06437 (US).
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(54) Title: DIFFERENTIALLY EXPRESSED GENES INVOLVED IN ANGIOGENESIS, THE POLYPEPTIDES ENCODED THEREBY, AND METHODS OF USING THE SAME

(57) Abstract: The present invention is directed to nucleic acid sequences and the polypeptides encoded thereby that are differentially expressed in angiogenesis. Also provided are methods for stimulating or inhibiting angiogenesis in mammals, including humans. Pharmaceutical compositions based on polypeptides, agonists, or antagonists thereto are also provided. Additionally, the invention also provides methods for diagnosing and treating angiogenic disorders including, but not limited to, wound healing and cancer.

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(21)出願番号	特願2001-535606(P2001-535606)	(71)出願人	キュラゲン コーポレーション アメリカ合衆国 コネチカット 06511, ニューヘブーン, ロングワード ライブ 555, 11ディーエイチ フロア ー
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(54)【発明の名称】 脈管形成に含まれる差動発現遺伝子、それにコードされるポリペプチド、及びそれを用いた方法

(57)【要約】

本発明は、核酸配列及びそれによりコードされるポリペプチドに係り、それらは脈管形成において差動的に発現される。また、ヒトを含む哺乳動物において脈管形成を刺激又は阻害する方法も提供される。ポリペプチド、それに対するアゴニスト又はアンタゴニストもまた提供される。さらに、本発明は、それらに限定されないが創傷治癒及び癌を含む脈管形成障害の診断及び治療のための方法も提供する。

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This image shows a full page of dot grid paper. It consists of multiple horizontal rows of small, evenly spaced black dots on a white background. The dots are arranged in straight lines across the entire width of the page, providing a guide for writing or drawing without solid lines.

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This image shows a full page of primary-ruled notebook paper. It features multiple sets of horizontal lines designed to help young learners write neatly. Each set consists of three lines: two solid horizontal dotted lines forming the top and bottom boundaries, and a dashed horizontal line in the middle to indicate where to form capital letters. The sets are repeated down the entire page, providing ample space for handwriting practice.

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Fig. 1A



Fig. 1B



Fig. 1C

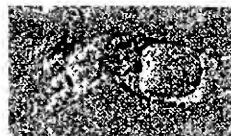


Fig. 1D



Fig. 1E



Fig. 1F

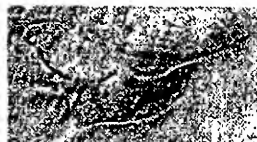


Fig. 1G



Fig. 1H

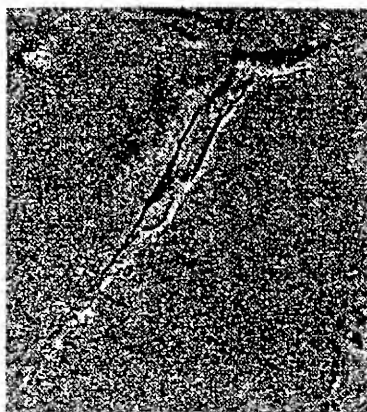


Fig. 1I

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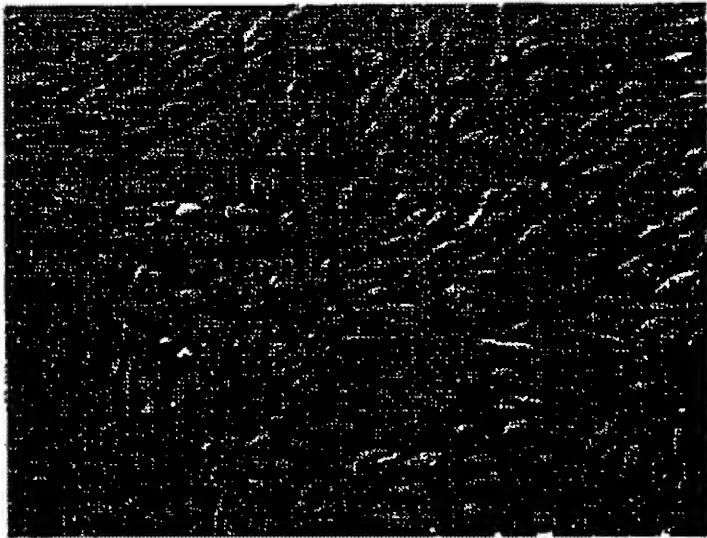


Fig. 1J

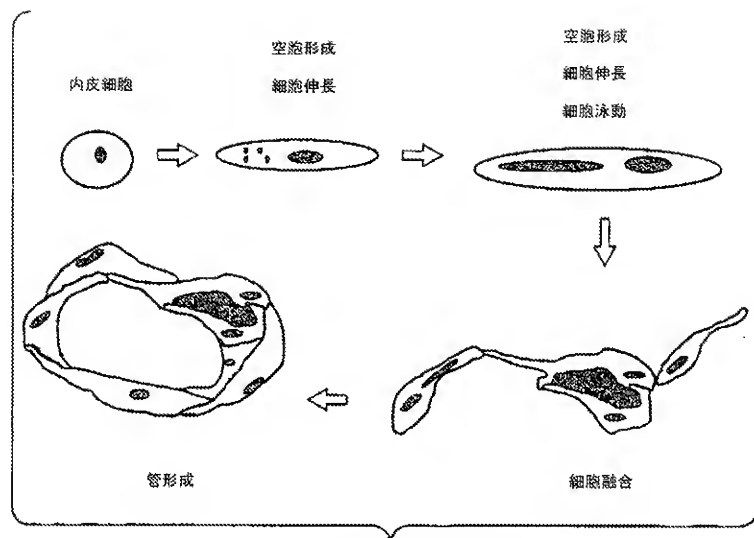


Fig. 2

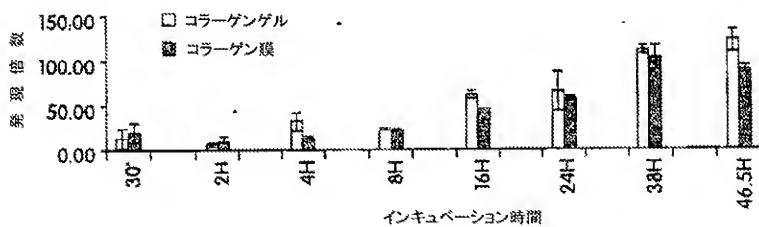


Fig. 3

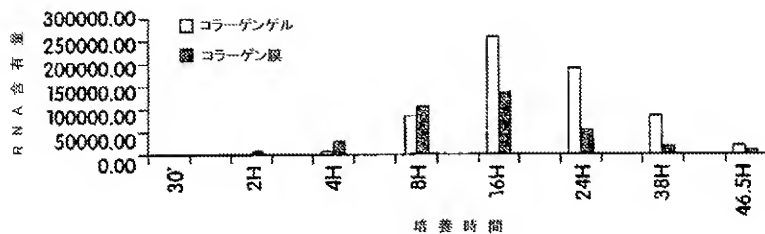


Fig. 4

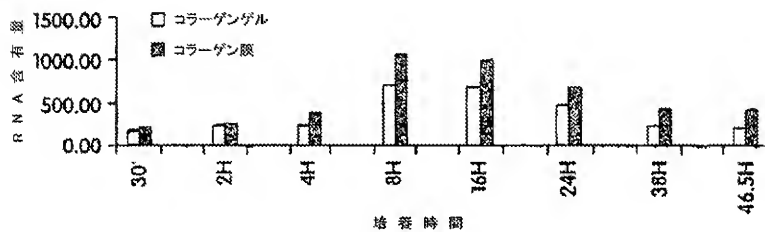


Fig. 5

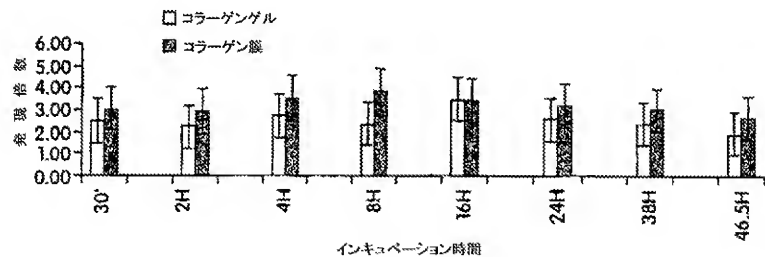


Fig. 6

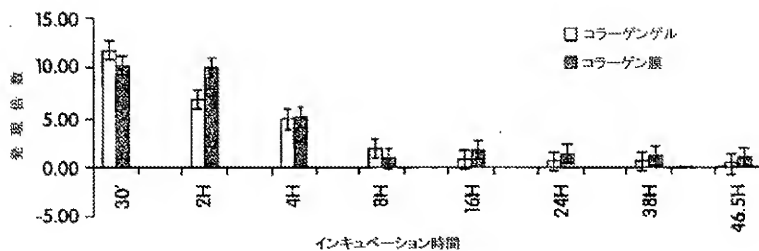


Fig. 7

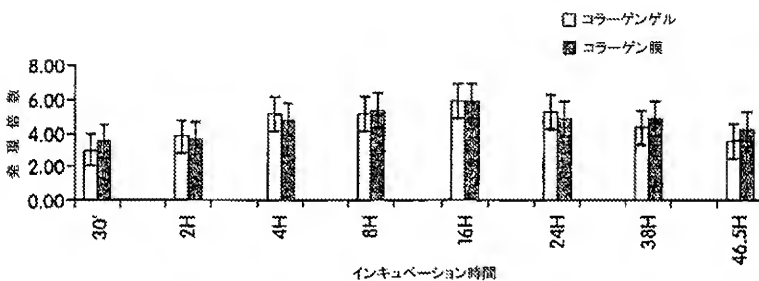


Fig. 8

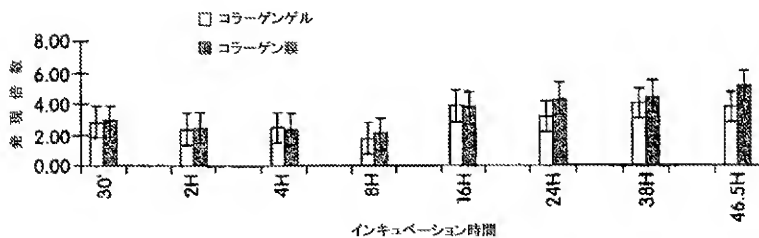


Fig. 9

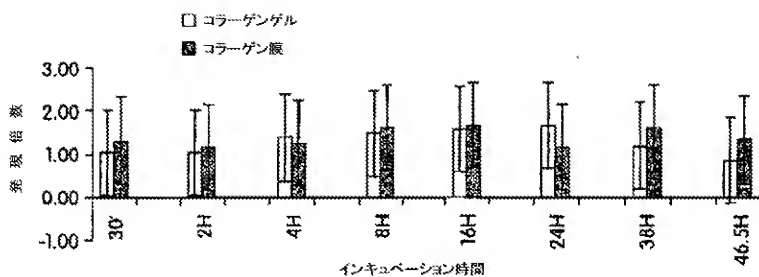


Fig. 10

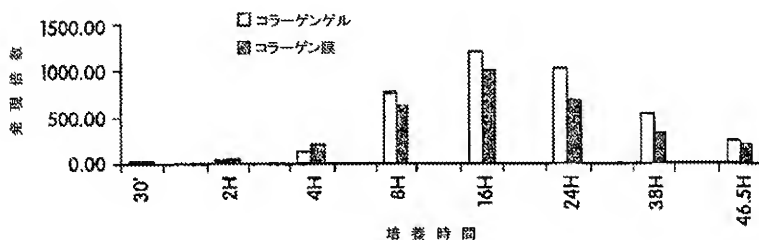


Fig. 11

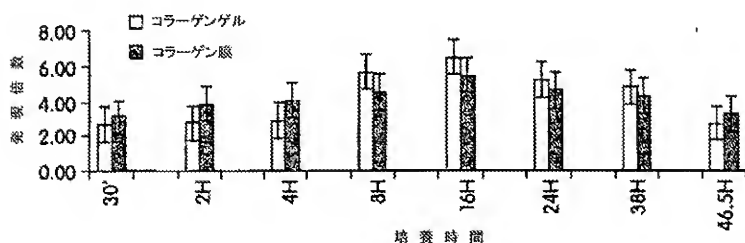


Fig. 12

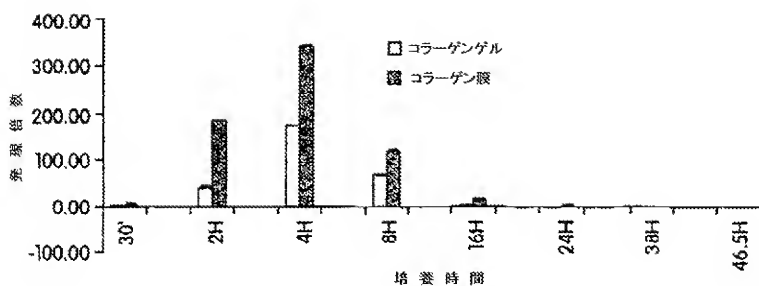


Fig. 13

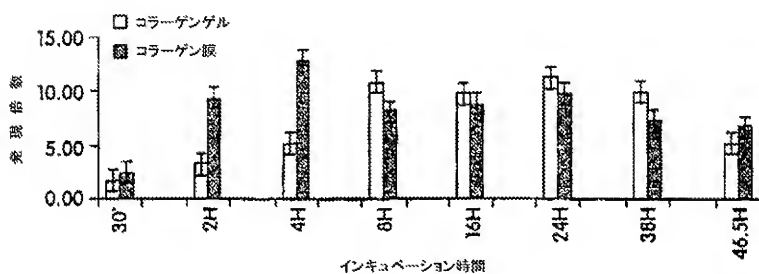


Fig. 14

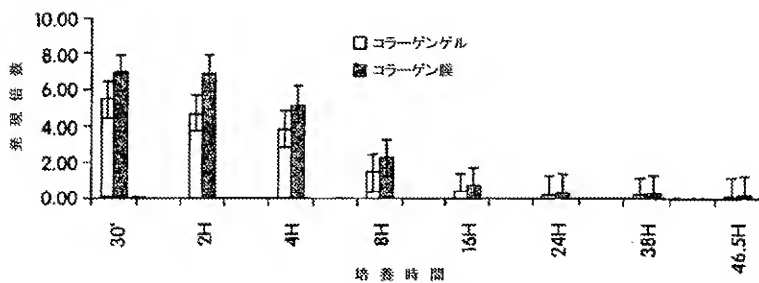


Fig. 15

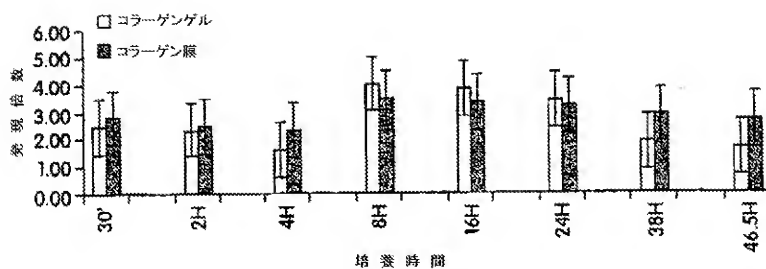


Fig. 16

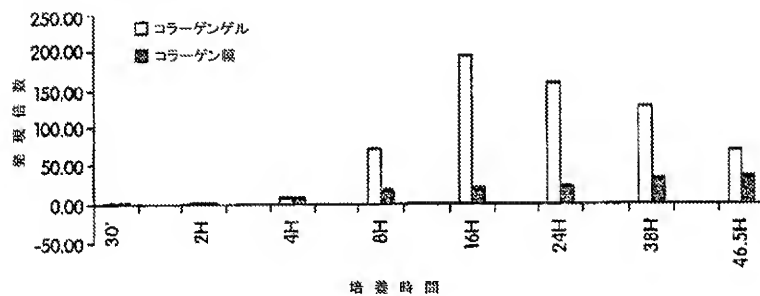


Fig. 17

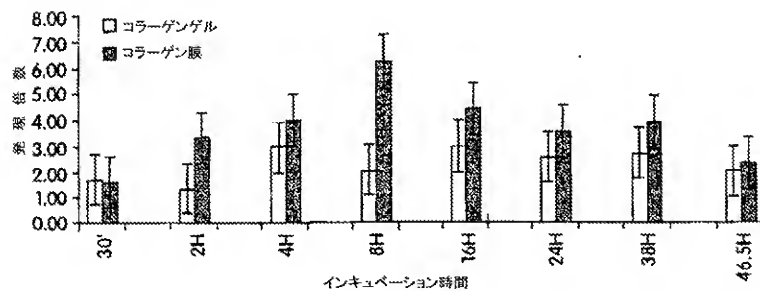


Fig. 18

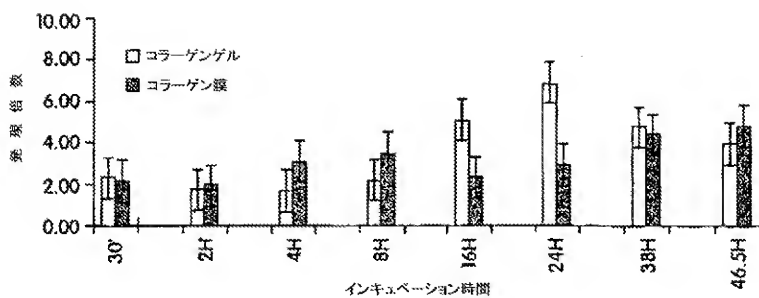


Fig. 19

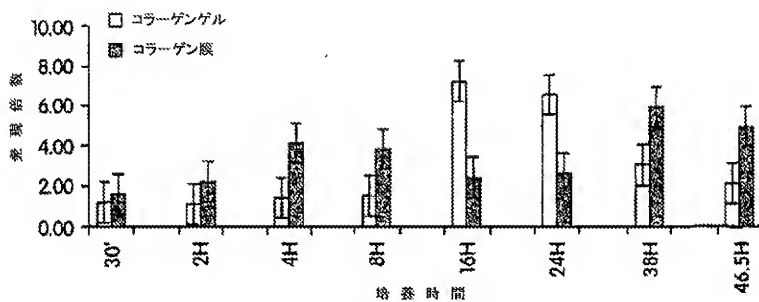


Fig. 20

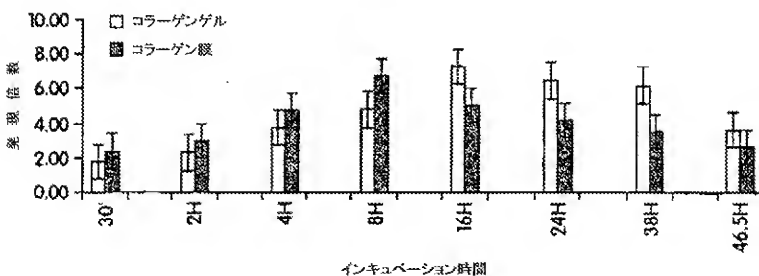


Fig. 21

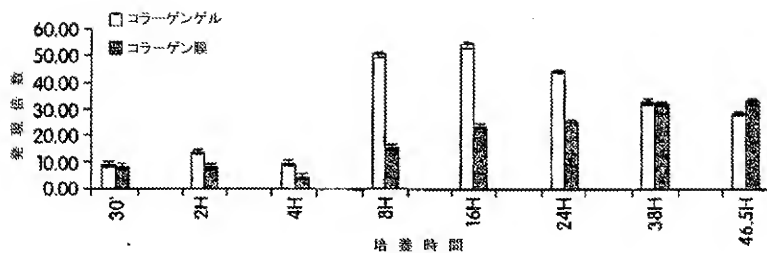


Fig. 22

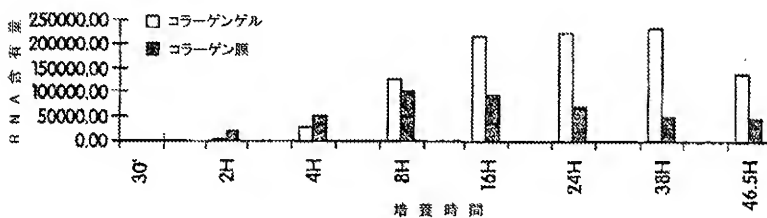


Fig. 23

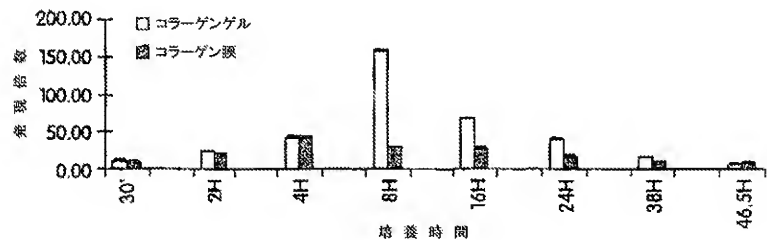


Fig. 24

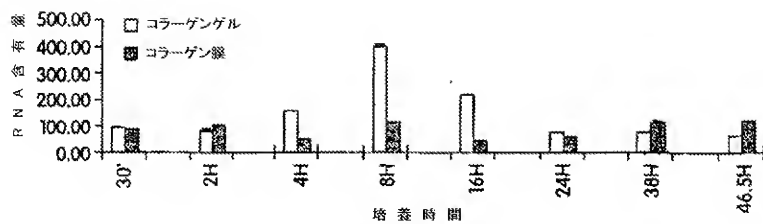


Fig. 25



Fig. 26

肺腺癌におけるDNA76510
(プロテインゼロ相同体)の発見

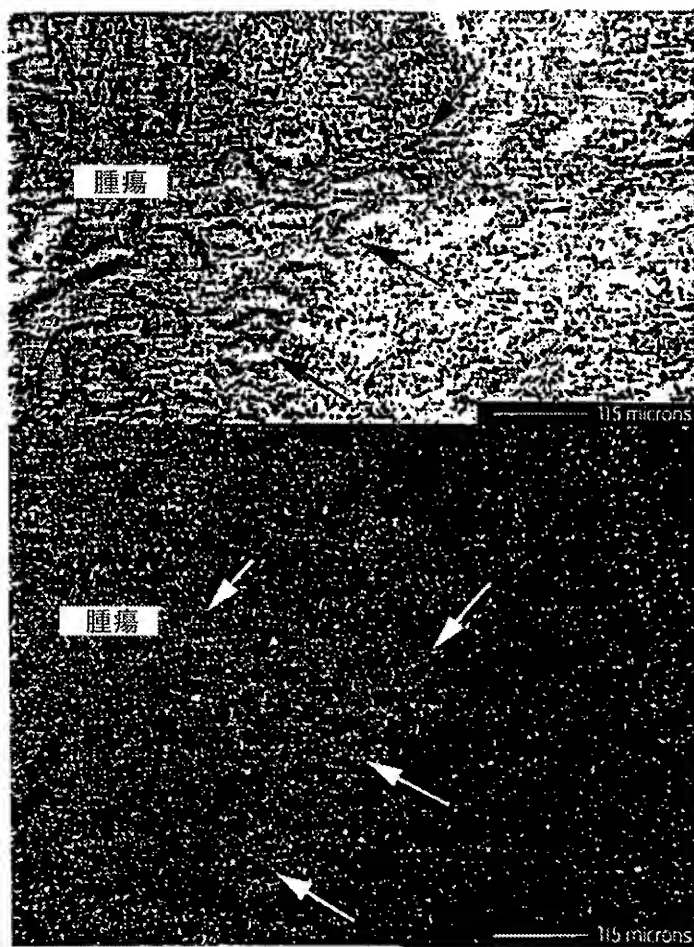


Fig. 27

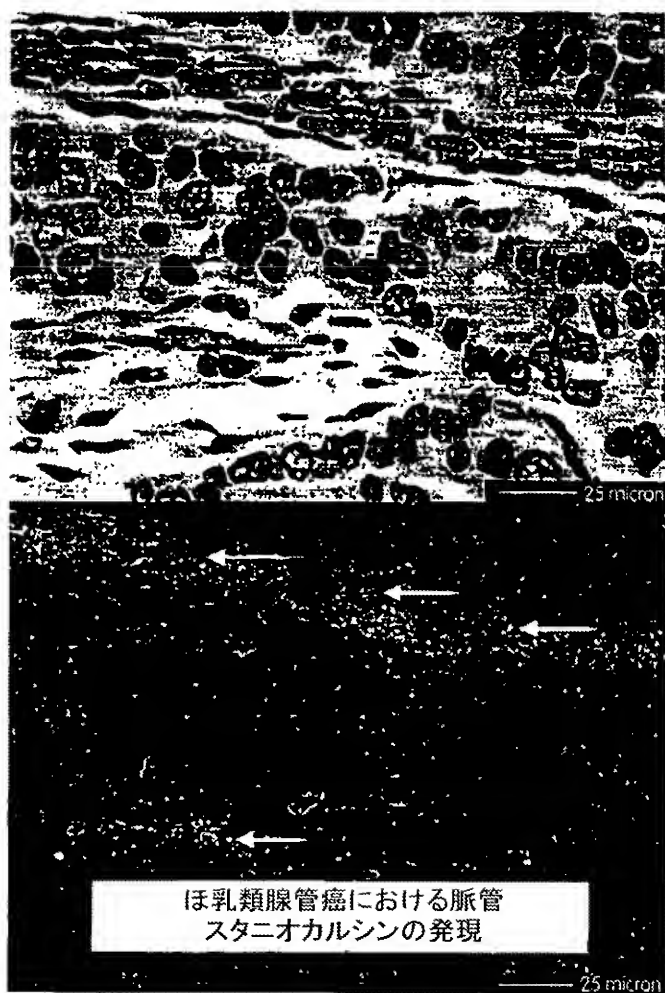


Fig. 28

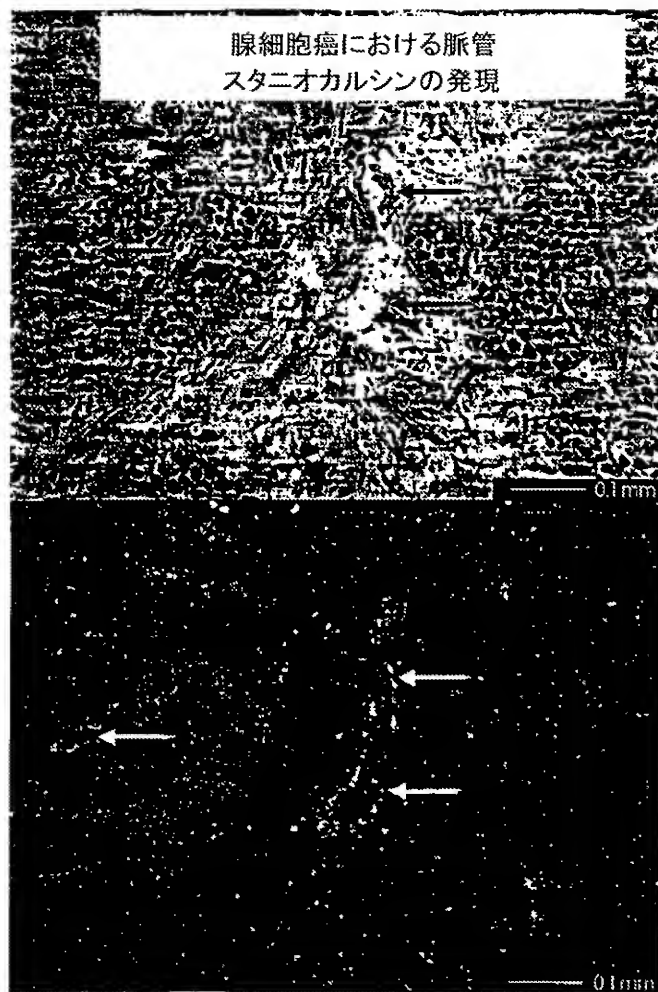


Fig. 29

1 MVGPA~~P~~RRL~~R~~PLA~~A~~LA~~V~~LA~~L~~APGLPTARAGOTPRPA~~R~~GE~~P~~VR~~L~~FTTE~~E~~LARYGGE~~E~~EDQPIYLA~~V~~KGVV~~F~~DVTSCKE
 81 FYGRGAPYNAL~~T~~GK~~D~~STRGVAKMSLDPADLTHD~~T~~TGLTAKELEALDE~~V~~FTK~~V~~YKAKYPIVGYTARRILNEDGSPNLD~~F~~K~~F~~P
 161 EDQPHFDIXDEF (配列番号: 72)

Fig. 30

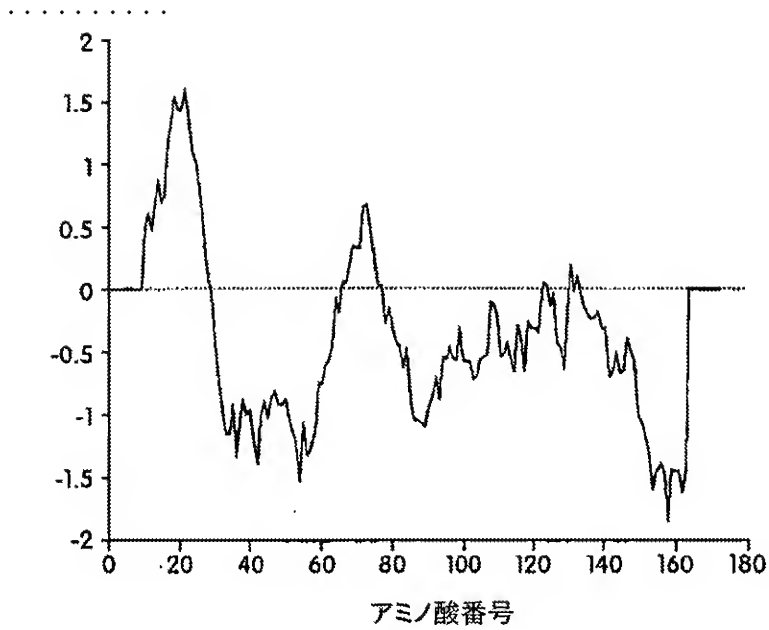


Fig. 31

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Sequence type explicitly set to Protein
Sequence format is Pearson
Sequence 1: 55193557_EXT      153 aa
Sequence 2: 11725372_EXT     161 aa
Sequence 3: AF173937         172 aa
Start of Pairwise alignments
Aligning...
Sequences (1:2) Aligned. Score: 83
Sequences (1:3) Aligned. Score: 83
Sequences (2:3) Aligned. Score: 90
Start of Multiple Alignment
There are 2 groups
Aligning...
Group 1: Sequences: 2      Score:1860
Group 2: Sequences: 3      Score:1948
Alignment Score 2458
CLUSTAL-Alignment file created [/data4/genetools/lrastelli5501clustalw]

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Multiple Alignment:

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55193557_EXT -----GAGCGPSA-DELTACLADP-DELTA-----
11725372_EXT -----DELTAVR-VLDELTACLADP-DELTA-----
AF173937      MVGPAPRRRLDELTAVR-VLDELTACLADP-DELTA-----
55193557_EXT -----DELTAVR-VLDELTACLADP-DELTA-----
11725372_EXT -----DELTAVR-VLDELTACLADP-DELTA-----
AF173937      MVGPAPRRRLDELTAVR-VLDELTACLADP-DELTA-----

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Fig. 32

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表1. 差動発現データ

遺伝子名	GenBank登録番号	GeneCalling モジュレーション	TaqMan モジュレーション
オステオニドゲン (PA1)	D86425	+4	+2
ラミニン ガンマー-2鎖 (PA2)	U31201	+18	+48
ボドカリキシン様タンパク質 (PA3)	U97519	+12	+2
モエシン (PA4)	M59066	+2	1
中皮クラチンK7 (T1型) (PA5)	X03212	-5	-10
ミオシン-1C (PA6)	U14391	+2	ND
T-プラスチン (PA7)	L05491	+2	1
アクチン細胞タンパク質 (PA8)	U09873	+2	+2
ダイニン軽鎖 (PA9)	U32944	+3	ND
C3VS相同体 (PA10)	Q28282に類似	+2	1
カデプシンB (PA11)	M14221	+3	+2
アダプター-4, ADAMTS-4 (PA12)	NM_005099	+18	+2
組織因子経路インヒビター-2 (PA13)	L27624	+9	+7
ウロキナーゼインヒビター (PA1-2) (PA14)	M31551	-19	-92
チロシンキナーゼ, レセプター-ax1, alt. (PA15)	P30530	-6	-15
スプライズ2 (PA16)			
チロシンキナーゼ, レセプター, 上皮細胞, ECK (PA16)	NM_004431	+3	+3
OX40 (PA17)	S76792	+18	+18
インターフェイシングシグナルトランスドューサー, gp130 (PA18)	M57230	+3	1
cd82 (PA19)	D28137	+12	+4
プロテインゼロ関連タンパク質 (PA20)	AF087020	+6	+6
アルファ-2インテグリン (PA21)	X17033	+13	+2
胎盤成長因子 (PIGF) (PA22)	X54936	+6	+5
スタニオカルシン前駆体 (PA23)	U25997	+14	+8
繊維芽細胞成長因子 (FGF-18) (PA24)	AB009391	+4	1
ホワイトプロテイン相同体 (PA25)	X91249	+3	-2
siwマウスAlix (AIG-2相互作用タンパク質) (PA26)	AJ005073に類似	+5	+2

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This image shows a full page of dot grid paper. It features multiple horizontal rows of small, evenly spaced black dots on a white background. The dots are arranged in straight lines across the entire width of the page, providing a guide for writing or drawing without solid lines.

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This image shows a full page of white paper with horizontal dotted lines, typical of primary school writing paper. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

表 2

薬名	薬剤標的	抗体標的	治療的蛋白質	遺伝子治療	iseaseMarka
オスロネオニドゲン(PA1)	XX	XX		XX	XX
ラミニン ガンゲンと類(PA2)	XX	XX		XX	XX
近アカリヤン 糖タンパク質 (PA3)	XX	XX		XX	XX
ミオニン (PA4)	XX	XX		XX	XX
中夜クラシス 7 (H型) (PA5)	XX	XX		XX	XX
ミオニン 1 C (PA6)	XX	XX		XX	XX
ミオニン 2 (PA7)	XX	XX		XX	XX
アタキン 糖タンパク質 (PA8)	XX	XX		XX	XX
タイニン 糖質 (PA9)	XX	XX		XX	XX
C3VS 糖質 (PA10)	XX	XX		XX	XX
カゲブニン 糖 (PA11)	XX	XX		XX	XX
アタレカナーゼ, adACTS-4 (PA12)	XX	XX		XX	XX
細胞因子経路インヒビター-2 (PA13)	XX	XX		XX	XX
クロキナーゼ インヒビター (PA14)	XX	XX	XX	XX	XX
チロシンキナーゼ, レビブ クー, ntr, スズワイズ 2 (PA15)	XX	XX	XX*	XX	XX
チロシンキナーゼ, レビブ クー, 上皮細胞, EIS (PA16)	XX	XX	XX*	XX	XX
OX40 (PA17)	XX	XX	XX*	XX	XX
インターフェロンβ ナットランズク ユー, gp130 (PA18)	XX	XX	XX*	XX	XX
cd82 (PA19)	XX	XX	XX*	XX	XX
プロテインゼン 糖タンパク質 (PA20)	XX	XX	XX*	XX	XX
アルファ-2 マイクログロブリン (PA21)	XX	XX	XX*	XX	XX
細胞成長因子 (P16F) (PA22)	XX	XX	XX	XX	XX
スチミキカルシウム前駆体 (PA23)	XX	XX	XX	XX	XX
細胞成長因子 (P16F) (PA24)	XX	XX	XX	XX	XX
ホリイブプロテイン 糖質 (PA25)	XX	XX		XX	XX
α1マウブ 111 (A1G-2 糖質) クラシス 7 (PA26)	XX	XX		XX	XX

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表 3

元の残基	例示の置換	好ましい置換
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

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This image shows a full page of dot grid paper. It features approximately 20 horizontal rows of small, evenly spaced black dots. The dots are arranged in straight lines across the width of the page, providing a guide for writing or drawing without solid lines. The background is white, and the overall appearance is clean and minimalist.

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This image shows a full page of dot grid paper. It features approximately 20 horizontal rows of small, evenly spaced black dots on a white background. The dots are arranged in straight lines across the width of the page, providing a guide for writing or drawing without solid lines.

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This image shows a single sheet of white paper with horizontal dotted lines, typical of primary-ruled notebook paper. The lines are evenly spaced and run across the width of the page. There are no margins, text, or other markings on the paper.

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表 4. Taqman プライマー及びプローブの組

遺伝子名	PA #	正方向プライマー	逆方向プライマー	プローブ
ホルモン/成長因子				
胎盤成長因子 (PIGF)	22	GAGTCTCTACGACGTTGG CACCTTTCGGGCTTCATCTTC (SEQ ID NO:3)	CGAATCCGGGCTCTGCGG (SEQ ID NO:5)	
ストニオカルシン前駆体 (SEQ ID NO:4)	23	CGAGTGGCGGCTCAAAAGSEQ CCGACGCGGACCTGTGAGA (SEQ ID NO:7)	TCAGCTGAAGTGGTTCCTTGGCTTCA (SEQ ID NO:8)	
繊維芽細胞成長因子 (SEQ ID NO:9)	24	CCTTAGCTGACTCCCGACGTT CTGCGACTTCCCTCGATT (SEQ ID NO:10)	CCTGAACGAGCGGCTGGGCGG (SEQ ID NO:11)	
16 (FGF-16)				
チロシンキナーゼレセプター				
bx1	15	GCATGAAGGAATTGACCAT TCTCTGCTTCAAGACCTGGGA (SEQ ID NO:13)	CAGACACCGATGAGCCTCATGACCTT (SEQ ID NO:14)	
上皮細胞チロシンキナーゼ (E.C.K)	16	GCCTGTTTACCAAGATTGACA GCTTCGAGTCTGCTGCTGSE (SEQ ID NO:15)	TTGGCCCGCATGAGATCACC (SEQ ID NO:17)	
他のレセプター/一価糖タンパク質				
OX40	17	CCAGCTCTCGACXCTTCTAGG GGTATGATGACATAGCTAA (SEQ ID NO:18)	CCTGATGGCTCTCCGGCT (SEQ ID NO:20)	
ポドカリキシン様タンパク質	3	GGCACTGGTAGGTTTCACTCT TTACGCCGACAGACCATGG (SEQ ID NO:21)	CCATGCGGAAAAGTTTCAACATTTCCAC (SEQ ID NO:23)	
アルブミン-2 インテグリン	21	CCAGAGCTCCCAAGGCTTTC CAGTGGTATTTTTCGGACAT (SEQ ID NO:24)	AGGACTAGATCAGAAATGCAAGTCCATCTTCA (SEQ ID NO:26)	
Gp130	18	ATCCGCGCAAGATGTTGAC ACCCTGATGATCAGTGGTGAG (SEQ ID NO:27)	ACAAGGCTTGCCTACTACCAAGTCTGCGA (SEQ ID NO:29)	
プロラクチン受容体関連タンパク質	20	TGCTGATATCTCAATTTCTGGA TTGATGCACTGTGTCAGAA (SEQ ID NO:30)	TGACTTGGGCAATTTATCTTTGCTAATCTCT (SEQ ID NO:32)	
CD82	19	CGACACCTGGGACAGGISEQ AGCTTCTCTCCACCAACCA (SEQ ID NO:33)	CAGTGGTCAAGGGCCCACTTCT (SEQ ID NO:35)	

プロラクチン-レセプター/モノマーレセプター

組織因子経路インヒビター-2 (TFPI-2)	13	CGATGCTGCTGGAGGATAG A (SEQ ID NO:34)	ACACTGGTGTCCACACTCAC T (SEQ ID NO:37)	AAAGTTCCAAAGTTGGCGGCTGC (SEQ ID NO:38)
アグレカナーゼ(ADAMTS4; KIAA0688)	12	ACTGGTGGTGGCAGATGACA (SEQ ID NO:39)	TCACTGTAGCAGGTAGCCCT T (SEQ ID NO:40)	A7GGCCGCATTCCACCGGTGC (SEQ ID NO:41)
カテプシンB	11	GAAGCCATCTGTACCGGATC (SEQ ID NO:42)	TCCGCCGACCTCCA (SEQ ID NO:43)	CCACACCAATGCCACACGTCAGC (SEQ ID NO:44)
ブラスミノーザン/アタチン-2 インヒビター-2 (M1-2)	14	GCAGCCACAGCTGCAGATA (SEQ ID NO:45)	CCTGTGGATGCAATTGC (SEQ ID NO:46)	TCCATTCACTCTTCCGCTCTCTCAGC (SEQ ID NO:47)
トランスボリン/チヤンセル ホワイトアブラサイン粗画体	25	CCCTTTCAGATCATGTTCCCA (SEQ ID NO:48)	GGACGGCTCCGACGTC (SEQ ID NO:49)	CCAGTACACGATGCTGCAAGTAGGCCA (SEQ ID NO:50)
細胞骨格/運動性 モエシン	4	ACTGGCGCCGAGACAATACA A (SEQ ID NO:51)	AATGCGCTGCTTGCTGTG (SEQ ID NO:52)	CCCTGCGCCAGATCCGGGC (SEQ ID NO:53)
アタチン細胞タンパク質	8	CCAGCTGCTACTTTGACATCG (SEQ ID NO:54)	CCATTGGACGCCCTCAGT (SEQ ID NO:55)	GATGCGCGGTCCACGCCA (SEQ ID NO:56)
T-アプラスチン	7	AATAAACAAGCCATGCTCCC (SEQ ID NO:57)	CCTTAAGCCATAAGCACTTCA C (SEQ ID NO:58)	TGCATGATTCGCAAGGTGAGCTATTTC (SEQ ID NO:59)
膜アンチリン-2	10	AAGCAGCTTCTGATGCAATTC (SEQ ID NO:60)	CGACACAGCCGCTTACAT (SEQ ID NO:61)	TCCGAGCCCAAGAACACGCCA (SEQ ID NO:62)
中間フィラメント 中皮ケラチンK7	5	CCCAGATCTCCGACATCTG (SEQ ID NO:63)	CGCATGATCCCTCCAG (SEQ ID NO:64)	CCAATGGACAAGTGTGCTCCCTGCTGG (SEQ ID NO:65)
細胞外マトリクス ラミニン-2 (ニヒインB2鎖)	2	CCTGACAGCCAGGTGTTTGA A (SEQ ID NO:66)	CGAATGAGCTGCTTTTGCAC (SEQ ID NO:67)	TGTATCCACAACAGCCGGGCTACTGTG (SEQ ID NO:68)
ニトグリン-2 (結合ドメイン)	1	AAAACTTAGAAGCTTTTGTG CGAAACTA (SEQ ID NO:69)	CCTTGACAGTTGGAGAAGCC A (SEQ ID NO:70)	AAATAATTTGGTCTTTCCCATCAGTCTGTGCA (SEQ ID NO:71)

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/30051

A. CLASSIFICATION OF SUBJECT MATTER	
IPC 7 C12Q1/68 C12N5/10	A61K39/00 C97K14/47 A61K48/00 G01N33/53 C07K16/18 C12N15/63
According to International Patent Classification (IPC) to both national classification and IPC	
B. FIELDS SEARCHED	
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07K C12Q	
Documents searched other than minimum documentation to the extent that such documents are included in the fields searched	
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) MEDLINE, SEQUENCE SEARCH, EPO-Internal	
C. DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Character of document with indication, where appropriate, of the relevant passages
A	<p>KOHFELDT E ET AL: "NIDOGEN-2: A NEW BASEMENT MEMBRANE PROTEIN WITH DIVERSE BINDING PROPERTIES" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB, vol. 282, 1998, pages 99-109, XP002928990 ISSN: 0022-2836 abstract; figures 1,5; table 1 page 103, right-hand column - page 104, left-hand column, paragraph 1 page 105, right-hand column - page 107, right-hand column; figures 7-9 --- -/-</p>
	Relevant to claim No. 1-30, 32-37, 39-42, 44-59
<input checked="" type="checkbox"/> Further documents are cited in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.	
<p>* Special categories of cited documents:</p> <p>(A) document defining the general state of the art which is not anticipated to be of particular relevance</p> <p>(E) earlier document but published on or after the international filing date</p> <p>(T) document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>(X) document relating to an oral disclosure, use, exhibition or other means</p> <p>(Y) document published prior to the international filing date but later than the priority date obtained</p> <p>(*) later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>(X) document of particular relevance: the claimed invention cannot be carried out novel or cannot be considered to "twinkle on horizon" step when the document is taken alone</p> <p>(Y) document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, each contribution being obvious to a person skilled in the art</p> <p>(*) document member of the same patent family</p>	
Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2002	02 07 2002
Name and mailing address of the ISA European Patent Office, P.O. Box 5818 Postfach 2 7111 - 22001 11111 Tel. (+31-70) 340-2000, Tx 31 051 ext 1, Fax: (+31-70) 340-3013	Authorized officer van Krompenburg, W

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/30051

C/(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indicator, where appropriate, of the relevant passages	Relevant to claim No.
A	BIRD IAN W ET AL: "Homophilic PECAM-1(CD31) interactions prevent endothelial cell apoptosis but do not support cell spreading or migration." JOURNAL OF CELL SCIENCE, vol. 112, no. 12, June 1999 (1999-06), pages 1989-1997, XP002193379 ISSN: 0021-9533 abstract	1-30, 32-37, 39-42, 44-59
A	WO 97 30065 A (MILLENNIUM PHARM INC) 21 August 1997 (1997-08-21) page 1, line 8 - line 27 page 10, line 23 - line 29 page 12, line 33 -page 13, line 6 page 57, line 23 -page 92, line 3 claims 12-69	1-30, 32-37, 39-42, 44-59
A	WO 98 31709 A (GERL MARTIN ;HOECHST AG (DE)) 23 July 1998 (1998-07-23) page 1; claims 34-42; example 7	1-30, 32-37, 39-42, 44-59
A	WO 93 23075 A (ONCOLOGIX INC ;UNIV OHIO STATE RES FOUND (US); LIANG CHI MING (US)) 25 November 1993 (1993-11-25) page 1 -page 2, line 3 page 40, line 25 -page 42, line 19 abstract; claims 1-39; example 9	1-30, 32-37, 39-42, 44-59
P,X	WO 00 52051 A (AVENTIS PHARMA GMBH) 8 September 2000 (2000-09-08) page 1, line 4 - line 24 claims 1-97; table 2	30,33, 34,37, 39-41, 47-59
P,X	WO 00 55174 A (HUMAN GENOME SCIENCES INC ;ROSEN CRAIG A (US); RUBEN STEVEN W (US)) 21 September 2000 (2000-09-21) page 1 -page 4 page 387, line 14 -page 399, line 27 seq id no 1 & 941 claims 1-23; tables 1,4	9-30, 32-37, 39-42, 44-59

Form PCT/ISA/210 (continuation of second sheet) (July 1993)

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 00/30051

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	<p>WO 01 73025 A (BETH ISRAEL HOSPITAL ; KALLURI RAGHURAM (US)) 4 October 2001 (2001-10-04)</p> <p>page 2, line 10 - page 6, line 6; claims 1-36; figure 1</p> <p>-----</p>	<p>30, 33, 34, 37, 39-41, 47-59</p>

Form PCT/ISA/210 (continuation of second sheet) (July 1982)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/30051

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.:
because they relate to parts of this International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependant claims and are not drafted in accordance with the second and third sentences of Rule 8.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-30, 32-37, 39-42, 44-59 partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-28, are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 30-34, 54-59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Present claims 30-34, 51-59 relate to a product defined by reference to a desirable characteristic or property, namely: a product that modulates the expression or activity of the nucleic acid of the invention.

The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products mentioned in the description at pages 41, lines 23-25, namely antibodies, antibody fragments, fragments or variants of PA polypeptides, peptides, antisense molecules.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 65.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1-30,32-37,39-42,
44- 59 partially

Invention 1 is characterized by Nidogen-2 (PA 1).
A method of assessing the efficacy of an angiogenic disorder treatment in a subject comprising identifying a difference in expression levels of PA 1. A method of diagnosing an angiogenic disorder. A method of identifying a test therapeutic agent. A method of diagnosing or determining the susceptibility to an angiogenic disorder. A method of treating an angiogenic disorder. A kit for detecting two or more nucleic acid sequences comprising PA 1. An array of probe nucleic acids, wherein said probes detect two or more nucleic acid sequences comprising PA 1. An isolated polypeptide used to treat an angiogenic disorder. An isolated nucleic acid used to treat an angiogenic disorder. A therapeutic composition comprising the above mentioned polypeptide and a carrier. A kit comprising a therapeutic composition. A method of treating an angiogenic disorder. A method for inhibiting angiogenesis. A method for stimulating angiogenesis.

Inventions 2-26: Claims 1-59 partially

The subject matter of the individual inventions 2-26 are characterized by the individual sequences of PA 2-26. Claims 31, 32, 38, 39 43, 44 are with the appropriate sequences (for instance: claim 31 with invention 5,14,15 for PA 5,14 and 15 respectively). Therefore, all of claims 1-59 belong all partially to a separate invention. The description of the subject matter is as for invention 1, but for the individual PA's.

Invention 27: claims 60-66 completely, claims 1-30,
33-37,40-42,45-59 partially

As for invention 1, but for PA 27 and additionally:
An isolated nucleic acid molecule that is at least 75% identical to a nucleic acid sequence encoding the polypeptide of SEQ ID NO: 27. A nucleic acid vector, a host cell, an isolated peptide, an antibody, a pharmaceutical composition. A method of detecting the presence of the above mentioned polypeptide or nucleic acid in a sample

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/US 00/39051

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9730055	A	21-08-1997	AJ 725192 B2 05-10-2000
			AJ 2124397 A 02-09-1997
			CA 2247246 A1 21-08-1997
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			WO 0055351 A1 21-09-2000

Form PCT/ISA/210 (subject to fee) (July 1997)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/36651

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0055174 A		WO 0055180 A2	21-09-2000
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		WO 0173025 A2	04-10-2001

Form PCT/ISA/210 (patent family annex) (July 1992)

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